PATENT SPECIFICATION

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COMPLETE SPECIFICATION

NO DRAWINGS

Pharmaceutical Compositions Comprising Drug/Resin Adsorbates

We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company of 124-184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel drug/resin adsorbate compositions useful in pharmacy.

Amprotropine, in the form of its salt with phosphoric acid [i.e. the phosphate of the *dl* tropic acid ester of 3-diethylamino-2,2-dimethyl-propanol-(1)], is a well known parasympatholytic agent which has been employed for many years as active ingredients in various pharmaceutical formulations marketed as antispasmodics and, to a limited extent, in antacid tablets as an antispasmodic ingredient. However, amprotropine phosphate is an extremely bitter-tasting substance, and this characteristic has limited the extent to which it can be incorporated in pharmaceutical formulations adapted for relatively prolonged or slow oral ingestion (e.g. ingestion by chewing, sucking, sipping or the like).

It has now been discovered that when a composition comprising amprotropine adsorbed on a nuclear sulphonic acid cation-exchange resin (hereinafter referred to as an amprotropine resinate) is coated with castor wax (that is to say a hydrogenated castor oil) not only is the resulting composition tasteless but the amprotropine content is not subject to hydrolysis during prolonged storage. Furthermore the amprotropine content is stable under many of the conditions of temperature and humidity which adversely affect the amprotropine resinate itself.

The novel compositions of the invention accordingly comprise a nuclear sulphonic acid cation-exchange resin in which at least some of the cations present are amprotropine cations and, as a coating therefore, castor wax.

Suitable ion exchange resins for practising the invention are particularly typified by the polymerized (vinyl-benzene)-containing nuclear sulphonic acid cation-exchange resins such as are disclosed for example in Patent Specification No. 577,707. Such resins, in a pharmaceutically acceptable micropowder form (i.e. of a size such that 95 per cent of the material passes through a 325 mesh screen; United States of America Standard Sieve Series), are especially useful for purposes of the present invention and are commercially available from the Rohm and Haas Co., Philadelphia, Pa., under their proprietary designation "AMBERLITE XE-69" ("AMBERLITE" being a registered trade mark). However, it will be obvious that highly acid cation-exchange resins other than the specific resin already referred to herein can be employed if desired.

The bulk amprotropine resinate which is employed for coating with hydrogenated castor oil to form the novel composition of the invention can conveniently be made by adding an aqueous solution of an amprotropine salt to the appropriate quantity of the nuclear sulphonic acid cation-exchange resin. It is usually convenient to employ the cation-exchange resin in its alkali-metal cycle; for example, the specific resin already referred to is supplied commercially in the sodium cycle and is advantageously used in this form. However, if desired, the cation-exchange resin can be reacted when it is wholly or in part in its hydrogen cycle. Similarly, since amprotropine is conveniently available in the form of its addition salt with orthophosphoric acid, it is advantageous to employ amprotropine phosphate as a starting material in the processes of the invention. However, it will be appreciated that the use

of other acid additon salts, especially water-soluble mineral acid addition salts, is within the purview of the invention. A satisfactory procedure for preparing the amprotropine resinate comprises agitating an aqueous solution of amprotropine phosphate at room temperature (i.e. *ca* 20°C) with the cation-exchange resin in its sodium cycle until the reaction mixture has reached equilibrium. Elevated temperatures can be employed but, ordinarily, there is no advantage in operating at a temperature above about 50°C. Usually it is preferred to effect the exchange reaction without external heating. In order to obtain a fairly high concentration of active ingredient in the amprotropine-loaded resin, it is usually desirable to continue the agitation until the concentration of amprotropine in the resin reaches at least 25 per cent by weight. Ordinarily, it is preferred to allow the exchange reaction to go to equilibrium and to reach a concentration of amprotropine in the resin of from about 34 per cent to 38 per cent by weight.

After the cation-exchange resin has been loaded with amprotropine, the reaction mixture is filtered and the loaded resin is dried (e.g. in an oven at 45°C or by exposure to a dry atmosphere at room temperature). Any agglomerations or lumps in the product can be broken up by grinding the dried product in a mill.

A preferred procedure for making the amprotropine resinate in bulk form comprises thoroughly agitating, at room temperature and for a period of several hours (e.g. from 5 to 10 hours), a desired quantity of the type XE-69 resin marketed under the registered trade mark "AMBERLITE" (micropowder, all in sodium cycle) with an aqueous solution of amprotropine phosphate containing about 2.0 millimols of amprotropine phosphate per gram of resin dissolved in a quantity of water equal to about 20 times the weight of the resin. After completion of the reaction, the amprotropine resinate is separated and preferably dried in an oven at 45°C for about three days and then ground in a mill of necessary. The amprotropine resinate is thus obtained in the form of a fine free-flowing amorphous powder.

The (castor wax)/(amprotropine resinate) composition of the invention is prepared by first melting the castor wax at a temperature in the range of about 90°C to 140°C (preferably about 100°C to 105°C) and adding the amprotropine resinate thereto with constant stirring. Castor wax in an amount of from about 50 to about 85 per cent by weight based on the total weight of the final (castor wax)/(amprotropine resinate) composition, preferably 60 to 75 per cent by weight, is employed. The resulting suspension of the amprotropine resinate in the melted castor wax is spray-chilled into an atmosphere which can be air, nitrogen or an inert gas. The spray-chilling can be carried out in conventional equipment using atomizing spray nozzles, such as a high speed centrifugal atomizing wheel, a centrifugal atomizing nozzle or a bifluid spray nozzle. The beadlets resulting from the spray-chilling step exist in the form of a fine, free-flowing, amorphous, tasteless, highly stable powder having a substantially spheroid shape and a particle size in the range of about 30 to 600 microns (preferably within the range of about 30 to 250 microns).

The (castor wax)/(amprotropine resinate) powder can be incorporated in liquid or solid pharmaceutical dosage forms by methods known *per se*. Such pharmacuetical compositions constitute an ancillary aspect of the present invention. Those containing a pharmaceutical adjuvant material in addition to the (castor wax)/(amprotropine resinate) are particularly adapted for slow oral ingestion by chewing, sucking or sipping. The (castor wax)/(amprotropine resinate) powder used for this latter purpose should not have a particle size over about 250 microns since with larger particles a "gritty" effect is felt in the mouth and the compositions are consequently less palatable. Accordingly, for these uses, the preferred range of particle size is very important.

The mixing of other pharmaceutically active ingredients with the (castor wax)/(amprotropine resinate) compositions can given rise to useful pharmaceutical compositions. Thus, useful antacid compositions are obtained by admixture of an acid-neutralizing ingredient and useful analgesic compositions are obtained by admixture of an analgesic ingredient.

The process of the invention is illustrated by the following examples:

Example 1.

Dissolve 810 g of amprotropine phosphate in 20 l of deionized water. To the solution add 1 kg of type XE-69 resin of registered trade mark "AMBERLITE" (or equivalent) of pharmaceutical grade, micropowder form (finer than 325 mesh) in its sodium cycle. Stir the suspension well for 6 hours at 25°C. Filter the mixture through a centrifugal filter. Wash the cake with 5 l of deionized water. Dry the washed cake in an oven at 45°C for 72 hours. Pass the dry resin through a FITZPATRICK-mill to break up lumps formed during drying.

Add 1 kg of the dry amprotropine resinate to 2 kg of melted castor wax maintained at a temperature of 100°-105°C. Stir the mixture thoroughly and spray-chill the resulting suspension using a high speed centrifugal atomizing wheel. The product is a fine, amorphous, highly stable tasteless powder.

Example 2.

To 50 g of amprotropine phosphate dis-

solved in 250 ml of water, add 30 ml of 25 per cent aqueous sodium hydroxide solution and 300 ml of chloroform. Extract the resulting amprotropine base in to the chloroform layer by shaking for 0.25 hours. Remove the chloroform layer and extract the base therefrom by shaking the chloroform layer with 300 ml of deionized water containing hydrochloric acid equivalent to the amprotropine base plus 5 per cent excess. Discard the chloroform layer. Filter the aqueous layer, adjust pH to 4.5 (approximately the pH of amprotropine hydrochloride) by adding sodium hydroxide solution and add deionized water to make up the total volume to 1500 ml. This solution contains 37.9 g of amprotropine base in the form of its hydrochloride.

Add 60 g of type XE-69 resin marketed under the registered trade mark "AMBERLITE" (pharmaceutical grade, micropowder form, all in sodium cycle) to the foregoing 1500 ml of amprotropine hydrochloride solution. Stir well for 1 hour. Filter off the amprotropine-loaded resin, and wash with 1 l of water. Dry at 45°C for 72 hours and mill. The resin is similar to that obtained in Example 1, but contains 29.6 per cent by weight of amprotropine.

Add 100 g of the dry amprotropine resinate to 196 g of melted castor wax maintained at a temperature of 100°-105°C. Stir the mixture thoroughly and spray-chill using a certifugal atomizing nozzle. The resulting product is similar to that of Example 1, but contains 10 per cent by weight of amprotropine.

Example 3.

Agitate 100 g of type XE-69 resin marketed under the registered trade mark "AMBERLITE" (of the same type employed in Examples 1 and 2) with 1000 ml of O.O5-*N* aqueous hydrochloric acid. Filter off the resin ,wash with 500 ml of deionized water and dry at 45°C for 72 hours. This processing puts a portion of the resin into the hydrogen cycle.

To a solution of 50 g of amprotropine phosphate in 250 ml of water add 25 ml of 25 per cent sodium hydroxide and 300 ml of chloroform. Shake the mixture in a separating funnel for 0.25 hours and remove the chloroform layer containing amprotropine base. Wash the chloroform layer with water or slightly acidified water until the wash water pH is 8.0 or lower. 50 ml of this chloroform solution contains 6.3 g of amprotropine base.

Stir 10 g of the previously processed resin (partially converted to the hydrogen cycle) with 50 ml of the foregoing chloroform solution of amprotropine for 0.5 hours. Filter off the amprotropine-loaded resin and wash with chloroform. Dry the washed resin at 45° for 24 hours. The amprotropine resin is similar to that of Example 1 but contains 34.9 per cent by weight of amprotropine.

Add 15 g of the dry amprotropine resinate to 28 g of melted castor wax maintained at a temperature of 100°-105°C. Stir the mixture thoroughly and spray-chill using a bifluid spray nozzle. The resulting product is similar to that of Example 1 but contains 10 per cent. by weight of amprotropine.

Example 4.

Stir 120 g of the type XE-69 resin marketed under the registered trade mark "AMBERLITE" (same kind as used in Example 1) with a solution of 100 g of amprotropine phosphate in 3 l of water, for 1 hour at 25°C. Filter off the amprotropine-containing resin and wash with 1 l of water. Dry the washed resin at 45°C for 72 hours. The resin is similar to that of Example 1 but contains 25.9 per cent by weight of amprotropine.

Add 200 g of the dry amprotropine resinate to 214 g of melted castor wax maintained at a temperature of 100°-105°C. Stir the mixture thoroughly and spray-chill using a bifluid spray nozzle. The resulting product is similar to that of Example 1 except that it contains 12.5 per cent by weight of amprotropine.

Example 5.

Proceed exactly as in Example 4 except stir the amprotropine-resin suspension for 1 hour at 45°C using a resin containing 25.6 per cent by weight of amprotropine. The final product contains 7.5 per cent by weight of amprotropine.

The manner in which the compositions of the invention may readily be made up into pharmaceutical formulations is illustrated by the directions contained in the following examples.

A) Granulate a mixture of 180 g of aluminium hydroxide, 320 g of magnesium trisilicate, 30 g of corn starch, 200 g of mannitol and 65 g of sucrose with a 40 per cent sucrose solution. After drying at 45°C for 48 hours and grinding through a No. 16 mesh screen, add 38 g of a (castor wax)/(amprotropine resinate) containing 10 per cent by weight of amprotropine adsorbed on the type XE-69 resin mentioned in the examples, 10 g of magnesium stearate and 10 g of powdered peppermint flavour. Mix well and compress into one thousand tablets. The formulation is for use as an antacid.

B) Exactly similar to A except that 76 g of the same (castor wax)/(amprotropine-resinate) is used as an antispasmodic ingredient.

C) Exactly similar to A except that 10 g of phenindamine tartrate is added to the granulation as an antiallergenic ingredient.

D) Granulate a mixture of 500 g of dihydroxy aluminium aminoacetate, 30 g of corn starch, 200 g of mannitol, 3.7 g of sodium *cyclo*hexyl sulphamic acid and 65 g

of sucrose with a 40% solution of sucrose. After drying at 45°C for 48 hours and grinding through a No. 16 screen, add 76 g of (castor wax)/(aprotropine resinate) in which the resin contains 10 per cent by weight of amprotropine as described in Example 1, 10 g of magnesium stearate and 10 g of powdered peppermint flavour. Mix well and compress into one thousand tablets —for use as an antacid.

E) Exactly similar to D except that 15 g of phenobarbitol is added as a sedative ingredient to the granulation and 38 g of the same (castor wax)/(amprotropine resinate) is used as the antispasmodic ingredient.

F) Granulate a mixture of 200 g mannitol and 200 g of 4X sucrose with 15% corn starch paste. After drying at 45°C for 48 hours and grinding through a No. 16 mesh screen, add 114 g of (castor wax)/(amprotropine resinate) in which the resin contains 10 per cent by weight of amprotropine as described in Example 1 and 5 g of magnesium stearate. Mix well and compress into one thousand tablets. This formulation is for use as an antispasmodic.

G) Exactly similar to F except that 15 g of phenobarbitol is added as a sedative ingredient to the granulation.

H) Granulate a mixture of 224 g of acetylsalicylic acid, 160 g of acetophenetidin, 30 g of caffeine and 100 g of 4X sucrose with 15% corn starch paste. After drying at 45°C for 48 hours and grinding through a No. 16 mesh screen, add 76 g of (castor wax)/(amprotropine resinate) in which the resin contains 10 per cent by weight of amprotropine as described in Example 1, 10 g of talc and 10 gm of "STEROTEX" lubricant. Mix well and compress into one thousand tablets. This formulation is for use as an analgesic.

J) Exactly similar to H, except that 10 g of phenindamine tartrate is added as an antiallergenic ingredient to the granulation.

K) Exactly similar to H, except that 10 g of phenindamine tartrate (an antiallergenic) and 5 g of phenylephrine hydrochloride (a decongestant) are added to the granulation for purpose of preparing one thousand analgesic or cold-treatment tablets.

L) Granulate a mixture of 150 g of dihydroxy aluminium aminoacetate, 3 g of sodium *cyclo*hexyl sulphamate and 30 g of corn starch with a solution of 40% sucrose and dry at 45°C for 48 hours. Granulate 320 g of acetyl-salicylic acid with 15% corn starch paste and dry at 45°C for 48 hours. After grinding both granulates through a No. 16 mesh screen, blend them together and add 38 g of (castor wax)/(amprotropine resinate) in which the resin contains 10 per cent by weight of amprotropine as described in Example 1, 10 g of talc and 10 g of "STEROTEX" lubricant. Mix well and compress into one thousand buffered analgesic tablets.

M) Granulate a mixture of 250 g of acetophenetidin, 150 g of 1,5-dimethyl-4-*iso*propyl-2-phenyl-pyrazolone-(3), 50 g of caffeine, 5 g of sodium *cyclo*hexyl sulphamate, 30 g of corn starch and 40 g of 4X sucrose with a 30% ethanol solution of "CARBOWAX" 6000, and dry at 45°C for 68 hours. Granulate a mixture of 30 g of methyprylon; 50 g of calcium silicate, and 10 g of corn starch with a 5% solution of mtehyl-cellulose (100 cps), and dry at 45°C for 45 hours. After grinding both granulates through No. 16 mesh screen, blend them together and add 76 g of (castor wax)/(amprotropine resinate containing 10 per cent by weight of amprotropine as described in example 1), 10 g of talc and 10 g of magnesium stearate. Mix well and compress into one thousand tablets. This formulation is for use as an analgesic.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition which comprises a nuclear sulphonic acid cation-exchange resin in which at least some of the cations present are cations of amprotropine and, as a coating therefor, castor wax.

2. A composition as claimed in claim 1, wherein said cation-exchange resin is a nuclear sulphonic acid (vinyl-benzene)-containing nuclear sulphonic acid cation-exchange resin.

3. A composition as claimed in claim 1 or claim 2, wherein said cation-exchange resin is in micro-powder form.

4. A composition as claimed in any one of claims 1, 2 or 3, wherein the castor wax is intimately admixed with from about 15 per cent to 50 per cent by weight of said cation-exchange resin containing amprotropine cations to an extent of from 25 per cent to 38 per cent by weight of said resin.

5. A composition as claimed in claim 4, wherein said cation-exchange resin is present in an amount of from about 25 per cent to 40 per cent by weight.

6. A pharmaceutical composition adapted for slow oral ingestion, which comprises a pharmaceutical adjuvant material in admixture with a composition as claimed in any one of claims 1 to 5 inclusive.

7. An antacid composition which comprises a pharmaceutical acid-neutralizing ingredient in admixture with a composition as claimed in any one of claims 1 to 5 inclusive.

8. An analgesic composition which comprises a pharmaceutical analgesic ingredient in admixture with a composition as claimed in any one of claims 1 to 5 inclusive.

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